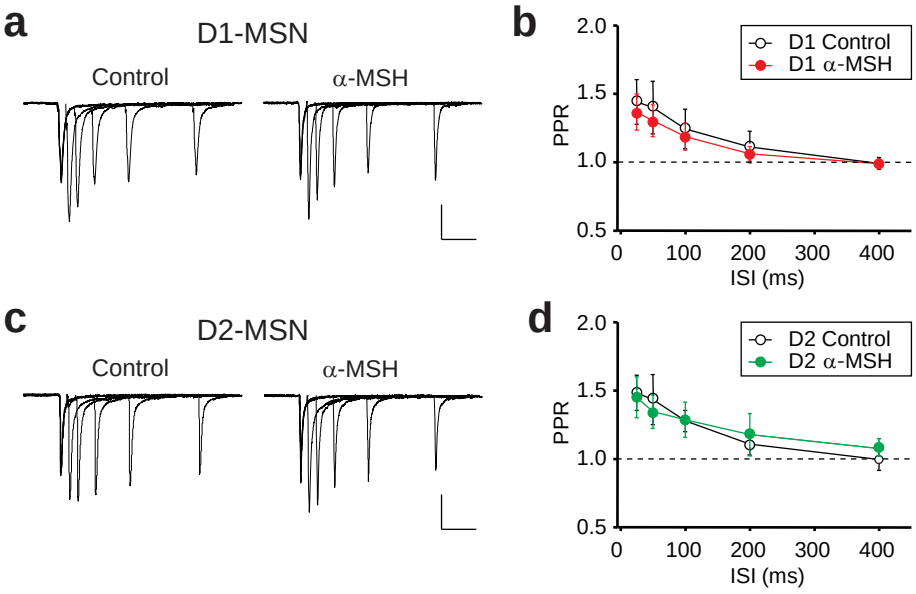
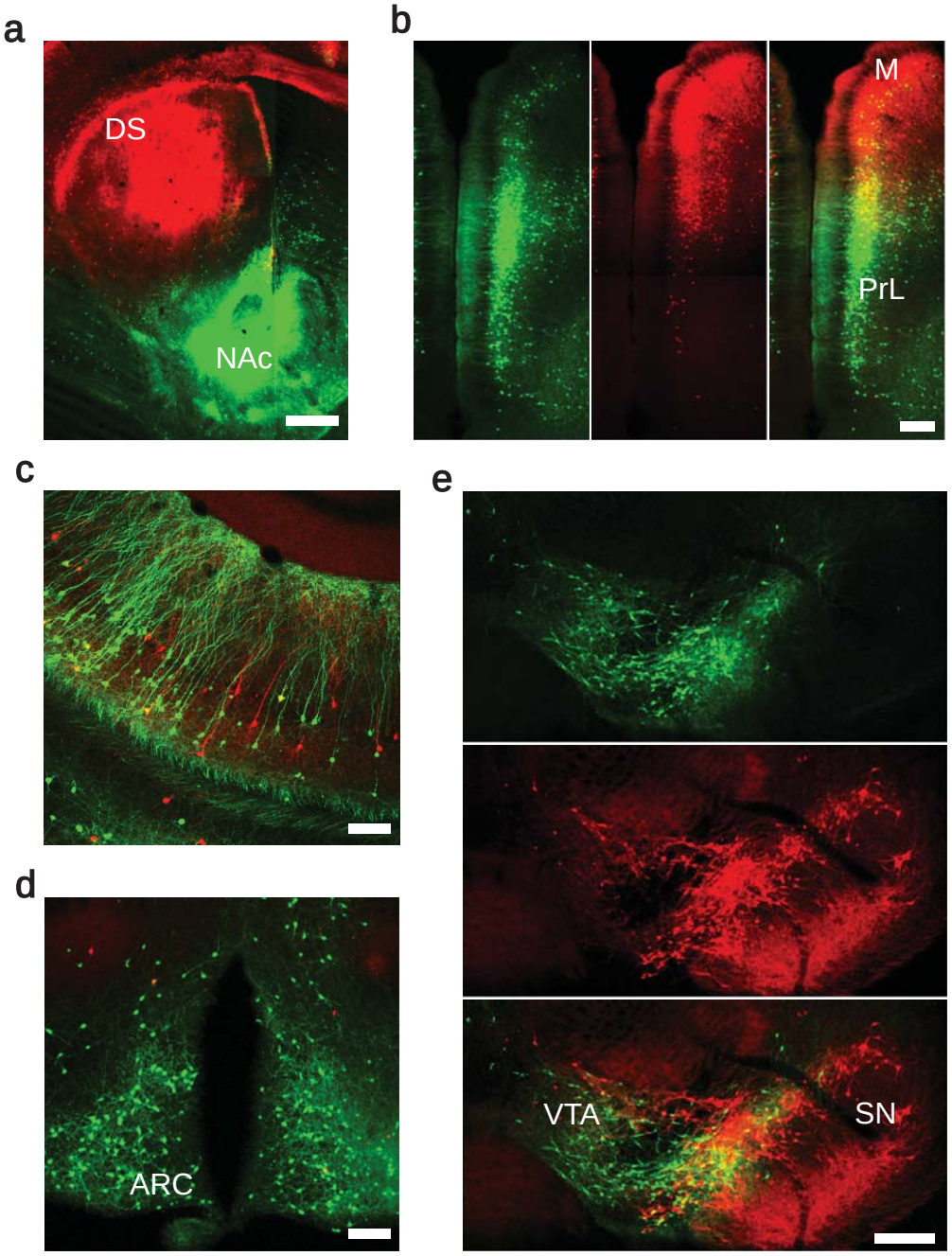
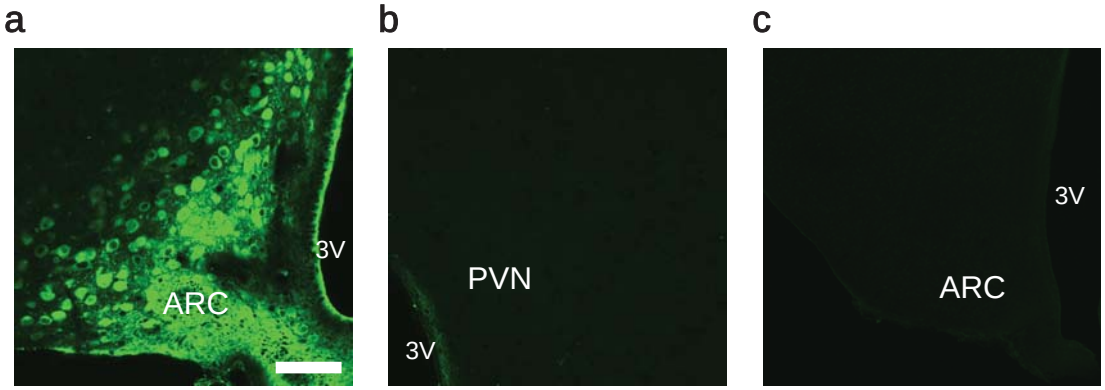


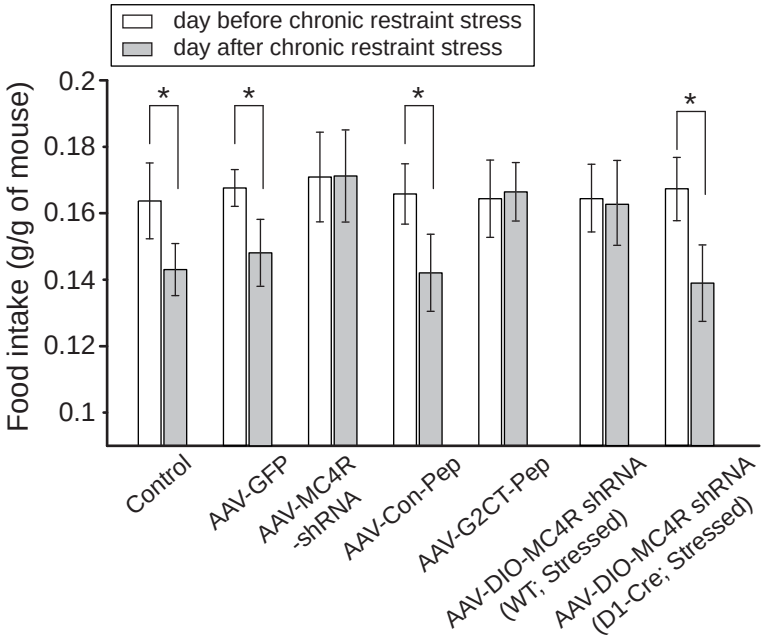
Supplementary Figure 1. The effect of α-MSH on paired-pulse ratios of excitatory synapses on D1-MSNs or D2-MSNs in the NAc. a, b, Sample EPSCs recorded from D1-MSNs (a) and summary graph (b) of paired-pulse ratios (PPR) at interstimulus intervals (ISI) of 20, 50, 100, 200 and 500 ms from control slices (*n* = 8) and slices incubated in α-MSH (1 μM) for 2-3 hours (*n* = 11). Scale bars: 70, 100 pA/100 ms. **c, d,** Sample EPSCs recorded from D2-MSNs (c) and summary graph (d) of PPRs from control slices (*n* = 7) and α-MSH treated slices (*n* = 9). Scale bars: 100, 120 pA/100 ms.



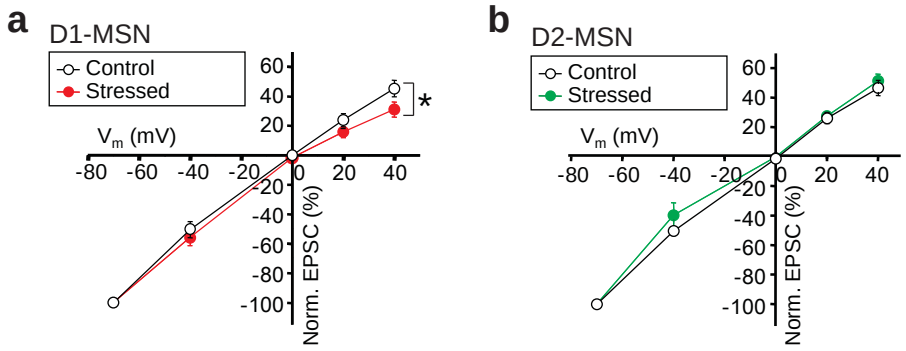
Supplementary Figure 2. Retrograde labeling of brain areas projecting to NAc or dorsal striatum using rabies virus. a, A confocal image of coronal section showing the injection sites in dorsal striatum (DS; RV-tdTomato) and nucleus accumbens core (NAc; RV-EGFP). Scale bar: 500 μm. **b,** A section of prefrontal cortex showing retrograde viral transport from NAc (left panel) or DS (middle panel) to prelimbic cortex (PrL) or motor cortex (M), respectively. Merged image (right panel). Scale bar: 500 μm. **c,** A section of ventral subiculum showing retrograde transport of EGFP and tdTomato from NAc and DS, respectively. Scale bar: 500 μm. **d,** A coronal section of arcuate nucleus (ARC) of hypothalamus showing retrograde transport of EGFP and tdTomato. Scale bar: 200 μm. **e,** Coronal sections of midbrain demonstrating retrograde transport of EGFP primarily to ventral tegmental area (VTA; top panel) and tdTomato primarily to substantia nigra (SN; middle panel). Merged image (bottom panel). Scale bar: 500 μm.



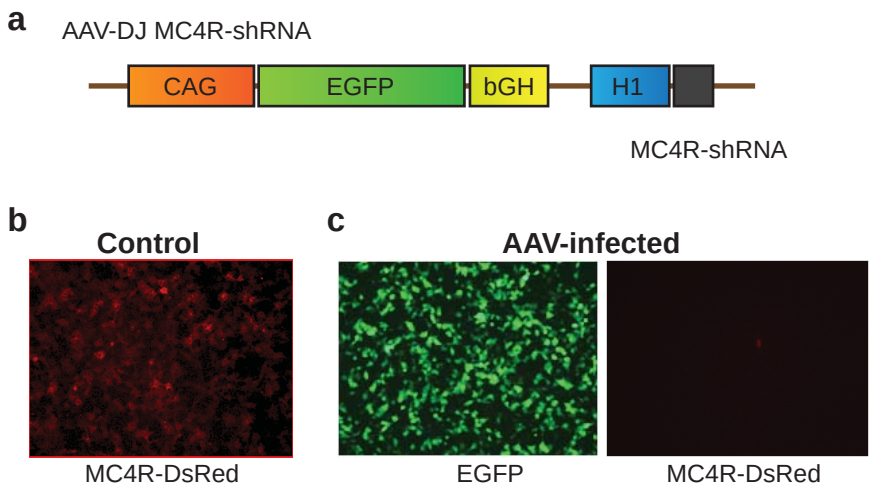
Supplementary Figure 3. Evidence for the specificity of the anti-α-MSH antibody staining in the arcuate nucleus of hypothalamus. a, Confocal image of coronal section showing α-MSH immunoreactive neurons in arcuate nucleus (ARC) (3V: 3rd ventricle; scale bar: 100 μm). **b,** Confocal image of coronal section showing that there are no detectable α-MSH immunoreactive neurons in the paraventricular nucleus of hypothalamus (PVN). **c,** Confocal image showing that pre-incubation of antibody with α-MSH completely prevents staining of α-MSH immunoreactive neurons in ARC.



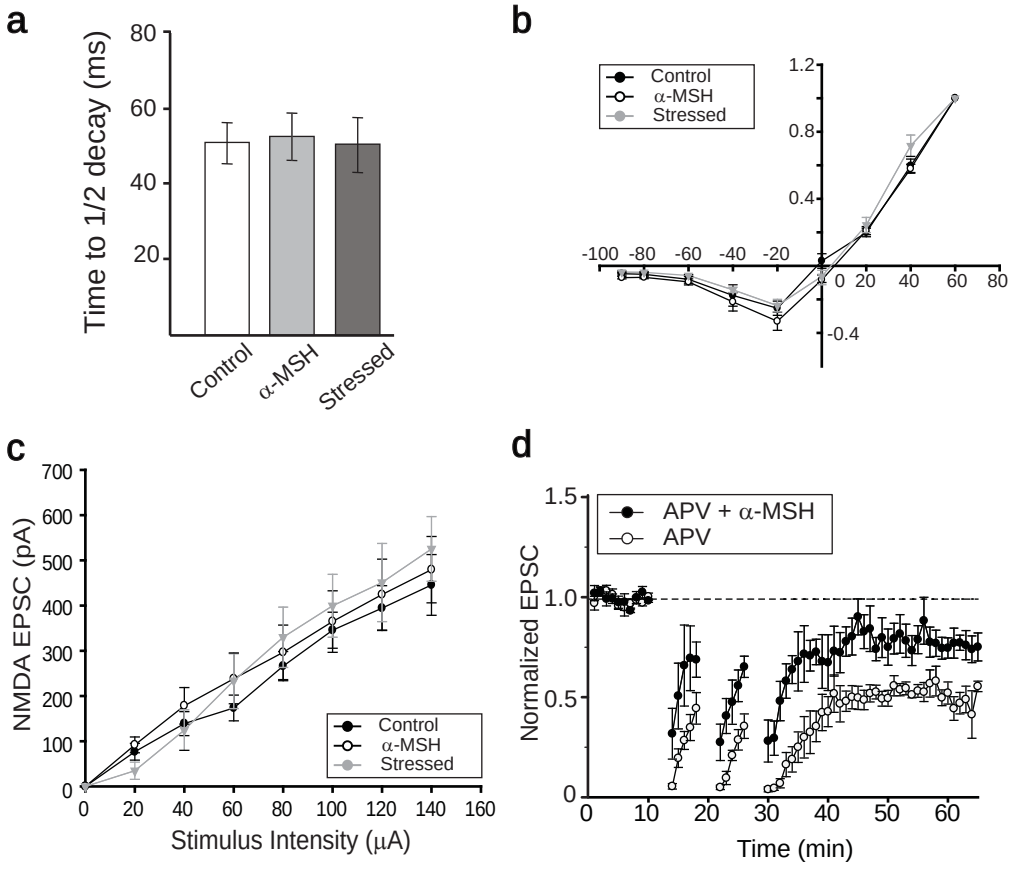
Supplementary Figure 4. Effect of chronic restraint stress on food intake. Summary of the food intake per 24 h per g of mouse measured before (left bars) and 8 days after restraint stress (right bars) in control mice (n = 9), mice which received NAc injections of AAVs expressing GFP alone (n = 9), MC4R shRNA (n = 10), the Con-Pep (n = 8), the G2CT-Pep (n = 10), AAV-DIO-MC4R shRNA (WT; Stressed; n = 6) or AAV-DIO-MC4R shRNA (D1-Cre; Stressed; n = 7). Note that expression of either the MC4R shRNA or the G2CT-Pep in the NAc prevented the stress-induced reduction of food intake in this test, and this effect was reversed by cell-type specific expression of MC4R (* $P < 0.05$ Mann-Whitney U-Test).



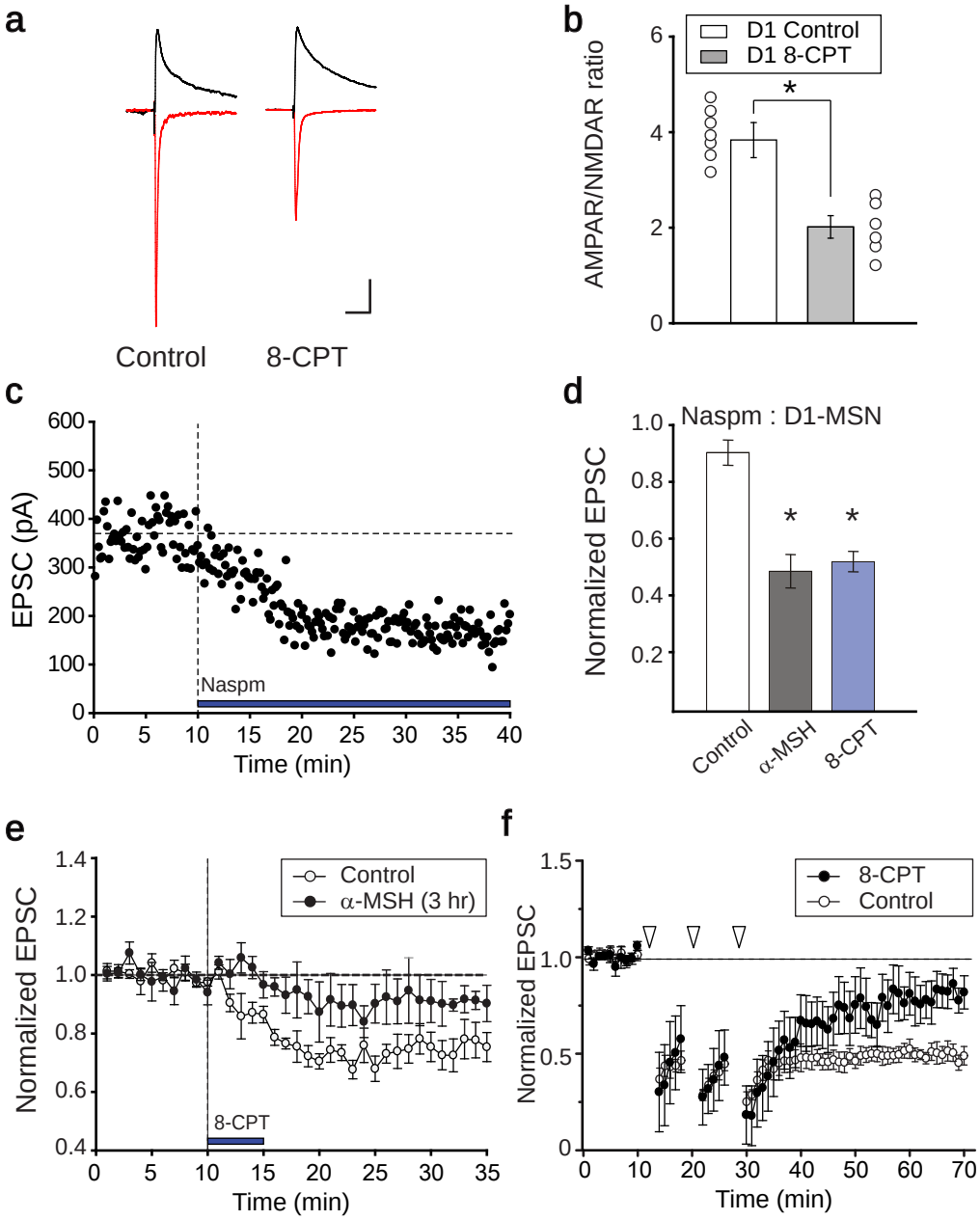
Supplementary Figure 5. Chronic restraint stress changes the stoichiometry of synaptic AMPARs in D1-MSNs but not D2-MSNs. Summary graphs of D1-MSN (a) or D2-MSN (b) AMPAR EPSC amplitudes at different membrane potentials.



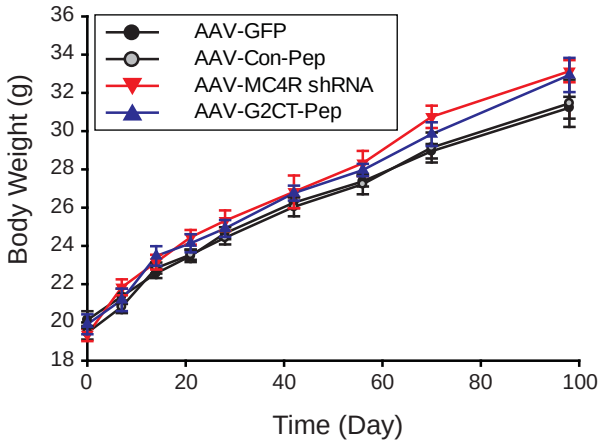
Supplementary Figure 6. Decrease of MC4R-DsRed fusion protein expression by shRNA against MC4R. a, Schematic of MC4R shRNA expressing AAV vector. **b,** Fluorescent image of HEK293 cells transfected with MC4R-DsRed expressing plasmid. **c,** Fluorescent images of HEK293 cells expressing MC4R-DsRed 48 hours after infection with AAV expressing MC4R shRNA and EGFP. Right panel shows significant reduction in the number of cells expressing MC4R-DsRed and the intensity of DsRed fluorescence.



Supplementary Figure 7. Properties of NMDAR EPSCs in D1-MSNs are unaffected by α-MSH application and chronic stress. a. The half-decay time of NMDAR EPSCs recorded at +40 mV in D1-MSNs is not affected by α-MSH or chronic stress**.** The half-decay time is defined as the time elapsed from the peak of the EPSC to one-half peak amplitude. (n = 5 in each group). **b.** The I-V relationship of NMDAR EPSCs in D1-MSNs is not affected by α-MSH or chronic stress (n = 4 in each group). **c.** The size of NMDAR EPSCs in D1-MSNs as a function of stimulation intensity (i.e. input-output curves) is not affected by α-MSH or chronic stress (n = 4 in each group). **d.** Summary graphs showing LTD in D1-MSNs from slices that were pre-incubated with APV alone or pre-incubated with APV and α-MSH. LTD was still reduced by α-MSH (Control, 51 ± 7% of baseline 40-50 min after start of induction protocol, n = 4; α-MSH, 78 ± 5%, n = 4; * P < 0.05 Mann-Whitney U-Test).



Supplementary Figure 8. 8-CPT modifies excitatory synapses on NAc D1-MSNs in a manner identical to the modifications elicited by α-MSH application and chronic stress. a-b. Sample of EPSCs recorded from D1-MSNs at -70 mV and +40 mV (**a**) and summary graph (**b**) showing the effect of 8-CPT on AMPAR/NMDAR ratios (Control, 3.87 ± 0.43, n =7; 8-CPT, 2.03 ± 0.32, n = 6; * $P < 0.05$, Mann-Whitney U-test). **c-d.** Representative experiment (**c**) and summary graph (**d**) showing the sensitivity of AMPAR EPSCs to Naspm after 8-CPT application (Control, n = 6; α-MSH, n = 8; 8-CPT, n = 4; * $P < 0.05$ compared to control, Mann-Whitney U-test)**. e.** Summary graphs showing that effects of 8-CPT on AMPAR EPSCs are reduced by prior exposure to α-MSH (Control, 75 ± 6% of baseline 20-25 min after start of 8-CPT application, n = 4; α-MSH, 92 ± 5%, n = 4; * $P < 0.05$ Mann-Whitney U-Test). **f.** Summary graphs showing LTD in D1-MSNs is reduced by prior exposure to 8-CPT (Control, 47 ± 4% of baseline 50-60 min after start of induction protocol, n = 7; 8-CPT, 77 ± 9%, n = 4; * $P < 0.05$ Mann-Whitney U-Test).



Supplementary Figure 9. Long term measurements of body weight in mice injected with AAVs. The body weights of chow-fed mice who received NAc injections of AAVs expressing GFP alone (*n* = 7), MC4R shRNA (*n* =8), the Con-Pep (*n* = 7) or the G2CT-Pep (*n* = 8) were monitored over the 100 days following the injections. Expression of MC4R shRNA and G2CT-Pep caused a small, insignificant increase in body weight after 70-100 days